REMARKS

Claims under Examination

Applicants acknowledge that claims 23-26, 28, 30-35, 37, and 127-129 are pending. The Office Action indicated that claims 33-35, 37, and 128 are drawn to a nonelected invention. By this Amendment and Response, claims 23 is amended, 24, 27, 29-31, 33-126 and 128-129 are canceled. The claims are canceled to expedite prosecution and such cancellations or amendments are made without prejudice to or disclaimer of the previously claimed subject matter.

I. Rejection Under 35 U.S.C. § 112, first paragraph

Claims 23-26, 28, 30-32, and 127 were rejected under 35 U.S.C. § 112, first paragraph as allegedly failing to comply with the written description requirement. Independent claim 23 is directed to a method of ameliorating symptoms of a condition associated with inflammation.

Where a claimed method entails the use of a compound but does not explicitly recite the compound, the specification must nevertheless demonstrate that the applicant possessed the claimed methods by sufficiently disclosing molecules capable of performing the claimed activity. *See Ariad Pharm., Inc. v. Eli Lilly & Co.*, 560 F.3d 1366, 1373 (Fed. Cir. 2009); *see also Univ. of Rochester v. G.D. Searle & Co.*, 358 F.3d 916, 926 (Fed. Cir. 2004). An adequate written description of a nucleic acid "requires precise definition, such as by structure." *Regents of the Univ. of Cal. V. Eli Lilly & Co.*, 119 F.3d 1559, 1566 (Fed. Cir. 1997).

The claims presented above are specifically directed to inhibiting expression of a nucleic acid of SEQ ID NO:1 using siRNA targeted against that sequence. Because each nucleotide in a polynucleotide sequence can pair with only its complementary nucleotide, the recitation of a

polynucleotide sequence provides the precise structure of its complementary sequence. Thus, the explicit recitation of polynucleotide sequences can satisfy the written description requirement with respect to claims directed to complementary sequences. The Federal Circuit has explained that "[g]iven the sequence of a single strand of DNA or RNA, it may therefore have become a routine matter to envision the precise sequence of a 'complementary' strand that will bind to it. Therefore, disclosure of a DNA sequence might support a claim to the complementary molecules that can hybridize to it." *Rochester*, 358 F.3d at 925. Such an approach is reflected in the USPTO's Written Description Training Materials. *See, e.g.*, Example 12 ("The specification discloses a messenger RNA (mRNA) sequence that encodes newly discovered growth factor (NDG): SEQ ID NO: 1. . . . Because the general knowledge in the art is that the binding of any full-length complement of a target mRNA to that target mRNA will inhibit its expression, the specification discloses the complete structure of one species within the genus of claim 1, i.e., the full-length complement of SEQ ID NO: 1.")

The present specification discloses molecules capable of reducing the level or activity of the NF-HEV peptide. The specification discloses polynucleotide sequences encoding human, murine, and canine NF-HEV. *See* SEQ ID NOs: 1-3 and ¶ [0175]. The specification refers to "nucleic acid molecules which are complementary to NF-HEV nucleic acids" and states that particularly preferred nucleic acid molecules include "a contiguous span of at least 12, 15, 18, 20, 25, 30, 35, 40, 50, 60, 70, 80, 90, 100, 150, 200, 500, 1000, or 2000 nucleotides of the sequences in SEQ ID NOs: 1, 2 or 3 or the complements thereof." ¶¶ [0182]-[0183]. The specification further states that inhibition of the expression of NF-HEV can be achieved by "providing antisense nucleic acid that inhibits transcription or translation of NF-HEV mRNA, or

small interfering RNAs that induces degradation of a NF-HEV mRNA." ¶ [0016]; *see also* ¶ [0354].

In particular, the specification notes that "antisense nucleic acids include antisense polynucleotides complementary to the full-length sense strand . . . or complementary to oligonucleotide fragments from at least about 15 to more than about 120 nucleotides" of a nucleic acid that encodes the NF-HEV polypeptide. ¶ [0355]; *see also* ¶¶ [0460]-[0463]. Likewise, the specification states that sequence-specific inhibition of the expression of NF-HEV can be achieved using siRNAs that "comprise oligonucleotides of at least about 15 to greater than about 120 nucleotides." ¶ [0373]. Even more specifically, Example 20 of the present specification refers to an experiment "designed to demonstrate that a small-interfering RNA (siRNA) specific to a portion of the coding nucleotide sequence for NF-HEV (SEQ ID NO: 1) can reduce the expression of the NF-HEV polypeptide and thereby reduce the amount of pro-inflammatory chemokines." ¶ [0453]. The oligonucleotides to be utilized in both Examples 20 and 21 are specific to one or more discrete or overlapping 21 consecutive base pair portions of the coding region of SEQ ID NO: 1. ¶¶ [0453]-[0459]. The declaration of inventor Jean-Philippe Girard confirms that siRNAs set forth in Examples 20 and 21 specifically reduced the level of NF-HEV, which, in turn, led to a reduction in the level of at least one pro-inflammatory chemokine, CCL2/MCP-1. *See* Girard Declaration, ¶¶ 6-7.

Therefore, for at least the reasons discussed above, Applicants respectfully submit that claims 23-26, 28, 30-32, and 127 are in compliance with the written description requirement. Applicants respectfully request that the rejection of claims 23-26, 28, 30-32, and 127 under 35 U.S.C. § 112, first paragraph be reconsidered and withdrawn.

II. Rejections Under 35 U.S.C. § 102

Claims 23-25, 28[1], and 30 were rejected under 35 U.S.C. § 102(b) as allegedly being inherently anticipated by International Publication Number WO 99/38881 ("Ruben"). Claims 23-25, 28, 30-31, 127 and 129 were rejected under 35 U.S.C. § 102(e) as allegedly being inherently anticipated by US Patent Application Publication 2007/0015145 ("Woolf").

"A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference." MPEP § 2131 (*quoting Verdegaal Bros. v. Union Oil Co. of California*, 814 F.2d 628, 631, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987)). The fact that a certain characteristic may be present in the prior art is not sufficient to establish the inherency of that characteristic. *In re Rijckaert*, 9 F.3d 1531, 1534 (Fed. Cir. 1993). "To establish inherency, the extrinsic evidence must make clear that the missing descriptive matter is necessarily present in the thing described in the reference." *In re Robertson*, 169 F.3d 743, 745 (Fed. Cir. 1999) (emphasis added); MPEP § 2112. The Federal Circuit has reiterated this point, noting that "anticipation by inherent disclosure is appropriate only when the reference discloses prior art that must necessarily include the unstated limitation." *Atofina v. Great Lakes Chem. Corp.*, 441 F.3d 991, 1000 (Fed. Cir. 2006) (emphasis added).

a. International Publication Number WO 99/38881 ("Ruben")

The Office Action indicates that Ruben inherently discloses the claimed step of identifying a subject having symptoms of a condition associated with chronic inflammation.

[1] Applicants believe that claim 28, which depends from claim 26, was mistakenly rejected under 35 U.S.C. §§ 102 and 103. Claim 26 was not rejected under 35 U.S.C. §§ 102 and 103. "A claim in dependent form shall be construed to incorporate by reference all the limitations of the claim to which it refers." 35 U.S.C. § 112, fourth paragraph. Thus, dependent claim 28 cannot be rejected over the prior art where its base claim (claim 26) was not rejected over the prior art.

Ruben states that SEQ ID NO: 35 is primarily expressed in smooth muscle and that the tissue distribution suggests that polynucleotides corresponding to this sequence may be useful for the diagnosis, prevention, and/or treatment of various diseases and disorders, including diseases of the gastrointestinal tract (e.g., hiatal hernia and inherited ulceretic disorders), vascular disorders, and metabolic disorders (e.g., Tay-Sachs disease, pheylkenonuria, galactosemia, porphyrias, and Hurler's syndrome). Ruben, pages 51-52. Patients suffering from a disease of the gastrointestinal tract (including an inherited ulceretic disorder) or a genetic metabolic disorder do not necessarily have symptoms of chronic inflammation. Therefore, the method of Ruben does not inherently or necessarily comprise the claimed step of identifying a subject having symptoms of a condition associated with chronic inflammation.

b. US Patent Application Publication 2007/0015145 ("Woolf")

The Office Action indicates that Woolf inherently discloses the claimed step of identifying a subject having symptoms of a condition associated with chronic inflammation.

Woolf mentions "a method of treating pain in an animal comprising administering to the animal an antisense polynucleotide capable of inhibiting the expression" of, at least, SEQ ID NO:11450. Woolf, ¶ [0066]. Woolf further states that "'pain' refers to several different types of pain, including physiological or protective pain, inflammatory pain that occurs after tissue damage, and neuropathic pain which occurs after damage to the nervous system." *Id.* at ¶ [0111] (emphasis added). Thus, the pain to be treated by the method mentioned in Woolf is not necessarily a symptom of chronic inflammation, but rather, may be the "result of accidental trauma (e.g., falling trauma, burn trauma, toxic trauma, etc.), congenital deformity or malformation . . . or other conditions which are not within the control of the animal experiencing

the 'pain'." *See, e.g.*, Woolf, ¶ [0119]. Indeed, as Woolf makes clear, an animal experiencing "pain" does not necessarily also have symptoms of a condition associated with chronic inflammation because "pain" includes pain arising from stimuli other than inflammation. Therefore, the method of Woolf does not inherently or necessarily comprise the claimed step of identifying a subject having symptoms of a condition associated with chronic inflammation.

For at least the reasons stated above, Applicants respectfully submit that claims 23-25, 28, and 30 are not anticipated by Ruben and claims 23-25, 28, 30-31, 127 and 129 are not anticipated by Woolf. Applicants respectfully request that the rejections of claims 23-25, 28, 30-31, 127 and 129 under 35 U.S.C. § 102 be reconsidered and withdrawn.

III. Rejection Under 35 U.S.C. § 103(a)

Claims 23-25, 28-31, and 127 were rejected under 35 U.S.C. § 103(a) as allegedly being obvious over Kasuya et al. (*Acta Neurochirurgica Supplement*, 2001, 77:13-16) in view of Orr et al. (*Current Opinion in Molecular Therapeutics*, 2000, 2:325-331). The Office Action asserts that Kasuya discloses a nucleic acid sequence, DVS 27, which encodes an mRNA and protein identical to SEQ ID NOs: 1 and 4, respectively.

"All words in a claim must be considered in judging the patentability of that claim against the prior art." MPEP § 2143.03 (*quoting In re Wilson*, 424 F.2d 1382, 1385, 165 USPQ 494, 496 (CCPA 1970)). In order to establish a *prima facie* case of obviousness, the prior art, including the understanding of one of ordinary skill in the art, must provide a complete teaching of all the claim limitations. *See, e.g., In re Royka*, 490 F.2d 981, 180 USPQ 580 (CCPA 1974); "Examination Guidelines for Determining Obviousness Under 35 U.S.C. § 103 in View of the

Supreme Court Decision in *KSR Int'l Co. v. Teleflex, Inc.*" Federal Register Vol. 72 No. 195 at 57528 (October 10, 2007).

None of Kasuya, Orr, or any combination thereof teaches or suggests the step of identifying a subject having symptoms of a condition associated with chronic inflammation. Kayusa only mentions that DVS 27 "could be involved in inflammatory events," but also concedes that the functional role of DVS 27 was not then known. *See* Kasuya, page 16, col. 2. Orr discloses that patent applications have been filed that are directed to antisense nucleic acids for specific molecules related to inflammation (namely, LFA3, TNF-α, and cyclooxygenase), none of which are NF-HEV. Neither Kayusa nor Orr teaches or suggests that NF-HEV is a mediator of, or even associated with, any symptom of a condition associated with chronic inflammation.

Even assuming, for the sake of argument, that each of the limitations are found in the prior art, the Office Action fails to articulate a reason to combine the references. *See KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 418 (2007) ("it can be important to identify a reason that would have prompted a person of ordinary skill in the relevant field to combine the elements in the way the claimed new invention does"). Indeed, even after *KSR*, "[i]t remains necessary to show 'some articulated reasoning with some rational underpinning to support the legal conclusion of obviousness.'" *Aventis Pharma Deutschland GmbH v. Lupin, Ltd.*, 499 F.3d 1293, 1301 (Fed. Cir. 2007) (*citing KSR*, 550 U.S. at 418).

The Office Action cites the teachings of Kasuya as providing "sufficient guidance/motivation to one of ordinary skill in the art to make an antisense agent against DVS 27 and use it to reduce or ameliorate inflammatory responses." Office Action, pages 8-9. However,

the Office Action mischaracterizes the teaching of Kasuya. The Office Action states DVS27 "is responsible for inflammatory events in hemorrhagic cerebral vasospastic arteries." *Id.* at page 9 (emphasis added). Such a conclusion is not reached, or even supported by, Kasuya.

Without providing supportive data, Kasuya indicates that the expression levels of DVS 27 change in response to inflammatory stimuli and concludes that DVS 27 "could be involved in inflammatory events." Kasuya, page 16, col. 2. Kasuya does not speculate whether DVS 27 has pro- or anti-inflammatory properties. Instead, Kasuya states that DVS 27's "functional role is still unknown." *Id.* Thus, Kasuya merely demonstrates that the expression of a particular compound, DVS 27, changes in response to unidentified "inflammatory stimuli," without any indication of the function of that compound. In contrast, the present specification demonstrates that NF-HEV has pro-inflammatory properties and that reducing the level or activity of NF-HEV ameliorates symptoms of a condition associated with inflammation. For example, the specification demonstrates that NF-HEV induces the expression of several pro-inflammatory chemokines, including CCL2/MCP1, and, conversely, that reducing the level or activity of NF-HEV reduces the level or activity of these pro-inflammatory chemokines. *See, e.g.*, paragraphs [0038], [0055], [0382], [0449], and [0452].

While the prior art, including Kasuya, may well have identified various orthologs of human NF-HEV, it was the teachings of the present invention that demonstrated that NF-HEV has pro-inflammatory properties and that reducing the level or activity of NF-HEV ameliorates symptoms of a condition associated with inflammation. Only with this teaching would a person of ordinary skill in the art be motivated to ameliorate symptoms of a condition associated with

inflammation by identifying a subject having symptoms of a condition associated with chronic inflammation and reducing in the subject the level or activity of the NF-HEV polypeptide.

Therefore, for at least the reasons discussed above, Applicants respectfully submit that claims 23-25, 28-31, and 127 are not obvious over Kasuya in view of Orr. Applicants respectfully request that the rejection of claims 23-25, 28-31, and 127 under 35 U.S.C. § 103(a) be reconsidered and withdrawn.

IV. New Matter Rejection

Claim 129 was rejected under 35 U.S.C. § 112, first paragraph as allegedly containing subject matter that was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time that the application was filed, had possession of the claimed invention. While claim 129 is cancelled herein, the following remarks are presented to the extent that the limitations of claim 129 have been incorporated into claim 23. The Office Action states that "there does not appear to be a written description for the claim limitation 'providing an siRNA'." Office Action, pages 9-10.

The present specification states that inhibiting the function or expression of NF-HEV can comprise "providing . . . small interfering RNAs that induces degradation of a NF-HEV mRNA." ¶ [0016]; *see also* ¶¶ [0354] and [0373]-[0377]. Thus, the specification as filed provides a written description for the claim limitation "providing an siRNA." Applicants respectfully request that the new matter rejection of claim 129 under 35 U.S.C. § 112, first paragraph should be reconsidered and withdrawn.

CONCLUSION

If the Examiner has additional questions or the Applicants can be of further assistance, the Examiner is invited and encouraged to contact the Applicants' attorney at the number below.

The Commissioner is authorized to charge any necessary fees or credit any overpayment to the Deposit Account of McAndrews, Held & Malloy, Ltd., Account No. 13-0017.

Respectfully submitted,

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/Nabeela R. McMillian, #43,363/
Nabeela R. McMillian
Registration No. 43,363
Attorney for Applicants
McANDREWS, HELD & MALLOY, LTD.
500 West Madison Street, 34th Floor
Chicago, IL 60661
Telephone: (312) 775-8000
Facsimile: (312) 775-8100